

Appl. No. 09/996,555  
Atty. Docket No. 8341  
Amdt. dated 7 June 2004  
Reply to Office Action of 23 September 2003  
Customer No. 27752

## REMARKS

### AMENDMENTS TO THE SPECIFICATION

The Specification has been amended at the paragraph beginning on page 7, line 11, to correct a typographical error, an inadvertent transposition. The correct range for the polymer ratio should be from "about 1:10 to about 10:1", obviously not from "about 1:10 to about 1:10", as such a "range" between identical ratios would not even be a range.

### AMENDMENTS TO THE CLAIMS

Claims 1-24 are pending in the application, with all claims standing presently rejected. Herein, Applicants amend Claims 1, 3-4, 11, 14 and 23-24; cancel Claims 12-13; and add new Claims 25-35, WHEREUPON Claims 1-11, and 14-35 remain to be examined. Authorization to pay the additional claims fees believed to be due is attached.

Claims 1 and 11 have been amended to more particularly point out and distinctly claim Applicants' invention by indicating that the outer coating is applied "directly" to the inner coating layer. Basis lies, at least, at Examples 1 and 2, beginning on page 11, of the Specification as originally filed.

Claims 1 and 11 have also been amended to more particularly point out and distinctly claim Applicants' invention by indicating that the "outer coating layer compris[es] an enteric polymer that begins to dissolve in an aqueous medium at a pH of less than about 7". Basis lies, at least, at page 6, lines 4-5, of the Specification as originally filed.

Claims 1 and 11 have also been amended to more particularly point out and distinctly claim Applicants' invention by deleting alternative film forming polymers and indicating preferred enteric polymers that comprise the outer coating. Basis lies, at least, at page 6, line 9 to page 7, line 17, of the Specification as originally filed, and within the claims as originally filed.

Claims 1 and 11 have also been amended to show proper antecedent basis, i.e. "outer coating layer" (Claim 1 only) and "said outer coating layer", and to improve the readability of the claim by bulleting and indenting the "wherein" elements of the claim.

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Claims 3 and 4 have been amended to more particularly point out and distinctly claim Applicants' invention by indicating preferred outer coating layer polymers in view of the amendments presented above to Claim 1.

Claim 14 has been amended to correct dependency in view of the cancellation of Claim 13 herein.

Claims 23-24 have been amended to bold-type the claim numbers being referred to in dependency, for consistency with the type face used in all of the other claims.

Claim 24 has been amended to correct the spelling of "consistent" therein.

Claims 12-13 are cancelled *without* prejudice.

Claim 25 has been added to more particularly point out and distinctly claim Applicants' invention by indicating that a preferred solid dosage form is "a compressed tablet". Basis lies, at least, at page 9, lines 7-9, of the Specification as originally filed.

Claims 26 and 31 have been added to more particularly point out and distinctly claim Applicants' invention by indicating preferred total weights for the solid unit dosage form. Basis lies, at least, at page 9, lines 11-14, of the Specification as originally filed.

Claims 27 and 32 have been added to more particularly point out and distinctly claim Applicants' invention by indicating preferred amounts for the 5-amino salicylic acid to be present in the solid unit dosage form. Basis lies, at least, at page 4, lines 22-25, of the Specification as originally filed.

Claims 28 and 33 have been added to more particularly point out and distinctly claim Applicants' invention by indicating preferred minimum thicknesses for the outer coating layer. Basis lies, at least, at page 6, lines 6-8, of the Specification as originally filed.

Claims 29-30 and 34-35 have been added to more particularly point out and distinctly claim Applicants' invention by indicating preferred minimum thicknesses for the outer coating layer. Basis lies, at least, at page 7, lines 11-17, of the Specification as originally filed.

It is believed these changes do not involve any introduction of new matter. Consequently, entry of these changes is believed to be in order and is respectfully requested.

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### NOVELTY

#### I. Iamartino

Claims 1-4, 8-14, and 19-24 are rejected under 35 USC §102(b) as allegedly being anticipated by US 5,171,580 [herein "Iamartino"]. Applicants have cancelled Claims 12-13 herein, and as such Applicants submit this rejection is now moot as applied thereto. Applicants respectfully traverse the rejection as applied to the remaining claims, as amended herein, for the reasons set forth below.

Iamartino discloses an orally administrable pharmaceutical preparation comprising three coating layers: an inner layer, an intermediate layer, and an outer layer (col. 3, Summary of the Invention). The inner layer comprises anionic polymers, including those derived from methacrylic acid and methyl methacrylate (col. 3, lines 37-39). The intermediate layer comprises gelling polymers including various cellulose or vinyl containing polymers (col. 3, lines 58-68). The outer layer comprises enter materials, including among others, acrylic polymers such as anionic copolymers derived from methacrylic acid and methyl methacrylate (col. 4, lines 21-29). Importantly, the intermediate layer "is applied directly onto the first inner layer" (col. 4, lines 1-2). Thus, beginning at the innermost layer and moving outwardly, Iamartino has a [methacrylic acid and methyl methacrylate polymer] → [gelling polymer] → [methacrylic acid and methyl methacrylate polymer] arrangement.

Contrastingly, Applicants invention requires a pharmaceutical composition in a solid unit dosage form for oral administration comprising two layers: an inner layer and an outer layer (Claims 1 and 11). The inner layer comprises methacrylic acid and methyl methacrylate polymers. The outer layer comprises methacrylic acid, methyl methacrylate, ethyl methacrylate, and polyvinyl acetate phthalate polymers. Importantly, the outer layer "is applied directly to the inner coating layer". Thus, beginning at the innermost layer and moving outwardly, the invention has a [methacrylic acid and methyl methacrylate polymers] → [methacrylic acid, methyl methacrylate, ethyl methacrylate, and polyvinyl acetate phthalate polymers] arrangement. The inventive arrangement does not permit an intermediate layer, e.g. one comprising a gelling polymer to come between the invention's inner and outer coating layers. Further, one cannot simply read out Iamartino's intermediate layer in an attempt to place Iamartino's outer layer adjacent to Iamartino's inner layer, as Iamartino clearly states that their intermediate layer is applied directly onto their inner layer.

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It is well settled that "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference, and that the elements must be arranged as required by the claim" (emphasis added). Applicants' claim requires a layer comprising [methacrylic acid, methyl methacrylate, ethyl methacrylate, and polyvinyl acetate phthalate polymers] to be applied directly to a layer comprising [methacrylic acid and methyl methacrylate polymers]. Iamartino cannot satisfy this requirement since their [methacrylic acid and methyl methacrylate polymers] layer must be coated with a [gelling polymer] layer. This clearly does not permit the elements (polymer layers) to be arranged as required by Applicants' claim, and as such, Applicants submit that Iamartino does not anticipate Claims 1 or 11 and those claims depending therefrom. Accordingly, Applicants submit that the rejection is improper and should be withdrawn.

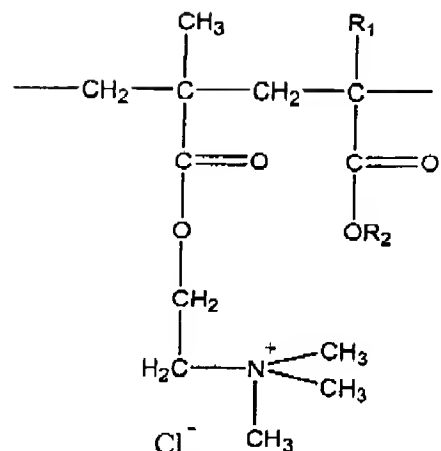
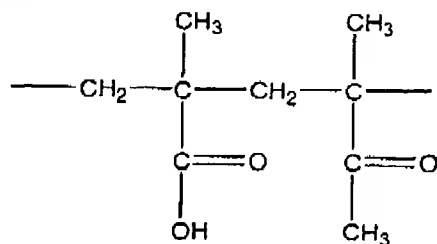
2. Rommelmayer

Claims 1-4, 8-9, 11-14, 19-20, and 22-24 are rejected under 35 USC §102(b) as allegedly being anticipated by WO 98/27,967 [herein "Rommelmayer"]. Applicants have cancelled Claims 12-13 herein, and as such Applicants submit this rejection is now moot as applied thereto. Applicants respectfully traverse the rejection as applied to the remaining claims, as amended herein, for the reasons set forth below.

Rommelmayer discloses an orally administrable pharmaceutical preparation comprising two layers: an inner coating and an outer coating (Abstract). The inner coating comprises enteric coating materials, including hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate or acrylic- and/or methacrylic acid/ester copolymers (page 10, line 34 to page 11, line 6). The outer coating comprises "a pH independent erodible film, which is penetrated and partly solubilized in the gastrointestinal tract" (page 11, lines 18-20 (emphasis added)), including ethyl cellulose, polysiloxane or polyethylene or copolymers of acrylic- and/or methacrylic acids/esters, e.g. EUDRAGIT RL or a mixture of EUDRAGIT RL and EUDRAGIT RS.

The layer-by-layer polymer arrangement of the present invention is described above. In contrast to Rommelmayer, Applicants' outer coating comprises certain enteric polymers "that begin[] to dissolve in an aqueous medium at a pH of less than about 7," i.e. they are pH dependent. Examples of such pH dependent polymers include EUDRAGIT L and EUDRAGIT S or mixtures thereof (page 7, lines 11-14). EUDRAGIT RL and EUDRAGIT RS polymers are not the same polymers as EUDRAGIT L and EUDRAGIT S polymers. For comparison, Applicants illustrate the polymers below (source: Handbook of Pharmaceutical Excipients, 2<sup>nd</sup> ed., Wade, Ainley, and Paul Weller, editors, pages 362-363, (1994), copy already provided to Examiner).

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where  $R_1 = H, CH_3$  and  $R_2 = CH_3, C_2H_5$

#### EUDRAGIT L and S

#### EUDRAGIT RL and RS

The EUDRAGIT RL and EUDRAGIT RS polymers (above, right) are copolymers synthesized from acrylic acid and methacrylic acid esters having functional quaternary ammonium groups (page 363, col. 1). The ammonium groups are present as salts and give rise to the pH independent permeability of the polymers (*id.*). In contrast, the EUDRAGIT L and EUDRAGIT S polymers (above, left) are anionic copolymerization products of methacrylic acid and methyl methacrylate (page 362, col. 2). These polymers are readily soluble in neutral to weakly alkaline conditions, i.e. they are pH dependent, and are soluble in intestinal fluid (*id.*). One cannot simply read the polymers' manufacturer's choice of nomenclature, e.g. use of "L", "S", "RL", and "RS" as being determinative of similarity between the polymers. Careful examination of the structures and characteristics reveals that they are quite dissimilar.

Rommelmayer fails to disclose an outer coating comprising an enteric polymer "that begins to dissolve in an aqueous medium at a pH of less than about 7." Instead, Rommelmayer requires that the polymer comprising the outer coating be "pH independent." As such, Rommelmayer does not set forth each and every element of Applicants' claims. Thus, Applicants submit that the rejection is improper and should be withdrawn.

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### NON-OBVIOUSNESS

1. Claim 15 in view of Rommelmayer

Claim is rejected under 35 USC §103(a) as allegedly being unpatentable over Rommelmayer. Applicants respectfully traverse the rejection for the reasons set forth below.

A. There is no teaching or suggestion to modify Rommelmayer to arrive at Applicants' invention.

The Examiner asserts that the skilled person would have found it obvious to substitute a mixture of EUDRAGIT S and EUDRAGIT L (Claim 15) for the mixture of EUDRAGIT RS and EUDRAGIT RL (Rommelmayer) because Rommelmayer suggests that the use of EUDRAGIT copolymers in the outer coating layer determines the release of the active agent.

While Rommelmayer does suggest the use of some EUDRAGIT copolymers in the outer coating layer, it specifically teaches away from using the type of EUDRAGIT copolymers employed in the present invention. As discussed above, EUDRAGIT S and EUDRAGIT L polymers are quite different from EUDRAGIT RS and EUDRAGIT RL polymers in their structure, properties, and function. Applicants' invention provides an outer coating that reduces the impact or negative effects of coating fractures. This outer layer addresses problems associated with the possibility of coating fractures that may occur during processing, manufacturing, or packaging of the solid unit dosage form. This layer requires an enteric polymer that begins to dissolve in an aqueous medium at a pH of less than about 7, i.e. it is pH dependent. This is so that the outer coating can begin dissolving in the gastric juice of the stomach, which is at a pH of less than about 7. Contrastingly, Rommelmayer's outer coating addresses prolonged release, the profile of which is dependent on the permeability and degradation of the coating material (page 13, lines 34-35). Rommelmayer's outer coating stays intact in the stomach and when it comes in contact with an aqueous medium it swells; over the time the solid unit dosage form is in the stomach and the intestine, this intact, permeable, outer coating acts as a diffusion barrier to release the active (*id.* at lines 29-34). Importantly, in order to achieve this, the outer coating must be pH independent (page 11, line 17).

For the skilled person to modify Rommelmayer's pH independent, intact, permeable, outer coating that swells when it comes in contact with an aqueous medium so that, instead, it comprises a pH dependent polymer that begins to dissolve in an aqueous medium at a pH of less than about 7 would be to modify Rommelmayer's solid unit dosage form in a way that would not

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permit prolonged release of the active, thus rendering it unsatisfactory for its intended purpose. As such, Applicants submit that the rejection is improper and should be withdrawn.

2. Claims 5-7 and 16-18 in view of Iamartino

Claims 5-7 and 16-18 are rejected under 35 USC §103(a) as allegedly being unpatentable over Iamartino. Applicants respectfully traverse the rejection for the reasons set forth herein.

Regarding Claims 5-6 and 16-17, while noting that Iamartino provides coating thicknesses in microns rather than milligrams per square centimeter, as Applicants do, the Examiner asserts that it would have been obvious to the skilled person to apply inner and outer coating layers of Applicants' thicknesses since Iamartino teaches that the thickness of the coating layers determines the quick dissolution of the coating layer (citing col. 3, lines 48-89). The Examiner further asserts that the skilled person would have been motivated to optimize the thickness of the coating layers determine in either set of measuring units with the expectation of producing desired quick dissolution of the coating layer. Regarding Claims 7 and 18, the Examiner asserts that Iamartino teaches coated actives cores or tablets and how the coated core is prepared is not critical in a formulation claim.

Applicants submit that neither the teaching of Iamartino generally, nor the passage cited by the Examiner, teaches or suggests an outer layer of any thickness, comprising [methacrylic acid, methyl methacrylate, ethyl methacrylate, and polyvinyl acetate phthalate polymers] and an inner layer comprising [methacrylic acid and methyl methacrylate polymers], where such an outer layer "is applied directly to the inner coating layer", nor does it teach or suggest the process for preparing such an arrangement. As such, Applicants submit that Iamartino fails to teach or suggest all claim limitations of Applicants' invention. In fact, at least because Iamartino requires its intermediate [gelling polymer] layer to be applied directly onto its first inner layer which comprises [methacrylic acid and methyl methacrylate polymer], Iamartino teaches away from Applicants' invention. Accordingly, Applicants submit that the rejection is improper and should be withdrawn.

3. Claims 23-24 in view of Rommelmayer and Claims 23-24 in view of Iamartino

Claims 23-24 are rejected under 35 USC §103(a) as allegedly being unpatentable over Rommelmayer and separately, as allegedly being unpatentable over Iamartino. Applicants respectfully traverse the rejections for the reasons set forth herein.

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The Examiner asserts that Rommelmayer and Iamartino each disclose orally administrable formulations with coating layers that determine the release of agents, that the skilled person would have been motivated to orally administer such formulations to the gastrointestinal tract.

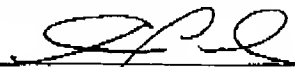
Applicants submit that neither the teaching of Rommelmayer or Iamartino teaches or suggests the oral administration to the gastrointestinal tract of a formulation comprising an outer layer comprising a pH dependent polymer that begins to dissolve in an aqueous medium at a pH of less than about 7, which are [methacrylic acid, methyl methacrylate, ethyl methacrylate, and polyvinyl acetate phthalate polymers] and an inner layer comprising [methacrylic acid and methyl methacrylate polymers], where such an outer layer "is applied directly to the inner coating layer". As such, Applicants submit that Rommelmayer and Iamartino each fails to teach or suggest all claim limitations of Applicants' invention. Accordingly, Applicants submit that the rejection is improper and should be withdrawn.

#### CONCLUSION

Applicants have made an earnest effort to place their application in proper form and to distinguish the invention as now claimed from the applied references. In view of the foregoing, Applicants respectfully request reconsideration of this application, entry of the amendments presented herein, and allowance of Claims 1-11, and 14-35. Early and favorable action in the case is respectfully requested. If there are remaining issues and the Examiner believes it would be prudent to do so, then she is invited to telephone the undersigned attorney to discuss them.

Respectfully submitted,

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